

IN THE SPECIFICATION:

Please amend the specification as shown:

Please delete the paragraph on page 2, line 34 to page 3, line 25 and replace it with the following paragraph:

The Rev-erb nuclear receptors form a subfamily of orphan nuclear receptors encoded by at least three different genes, Rev-erb α (earl), Rev-erb β (BD73, ear4, RVR) and HZF-2 (Rev-erb γ) (18-25), the natural ligands of which are currently unknown. The mRNA coding for the Rev-erb α nuclear receptor is expressed in many tissues, particularly in muscle, brown adipose tissue and the brain (26). Expression of the Rev-erb α gene is induced during adipocyte (26) and myocyte (53) differentiation and in the liver in response to a chronic treatment with fibrates (59). This expression also appears to follow a circadian rhythm (55). The two genes Rev-erb β and Rev-erb γ are expressed in particular in the brain (22, 25). Rev-erb α and Rev-erb β can bind as monomers to a response element consisting of a half-site PuGGTCA preceded by an A/T-rich region of 5 base pairs (A/T-A-A/T-N-T-A/G-G-G-T-C-A (SEQ ID NO: 30)) (28, 21). A dimeric binding of Rev-erb α on a direct repetition of two AGGTCA half-sites separated by two base pairs and preceded by an A/T-rich region has also been described *in vitro* (29). The crystallographic structure of the complex formed from the DNA binding domain of Rev-erb α with the direct repetition of the two AGGTCA half-sites has been described (54). In contrast with what had initially been described (28), it appears that the nuclear receptors of the Rev-erb subfamily repress the transcription (29, 20). Several physiological targets of Rev-erb α have been identified to date: the oncogene N-myc (30), the rat apo A-I gene (27), the human hRev-erb α nuclear receptor itself (31) and the transcription factors myoD and myogenin (53).

At page 13 of the specification, just before the “METHODS” section, please insert the following:

BRIEF DESCRIPTION OF THE DRAWINGS

Various features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood when considered in conjunction with the accompanying drawings, in which like reference characters designate the same or similar parts throughout the several views, and wherein:

Figure 1 shows that when HepG2 cells are cotransfected with a plasmid which comprises the

fragment (-1415/+24) of the human apo C-III promoter upstream of the luciferase reporter gene (-1415/+24WThCIILuc+) and the plasmid pSG5-hRev-erba which allows exogenous expression of the Rev-erba nuclear receptor, a 50% reduction in the activity of the reporter gene is observed.

Figure 2 shows that the activity of two heterologous promoters, the promoter for the thymidine kinase gene of the herpes simplex virus (noted as TkpGL3), or the major late promoter of the SV40 virus (noted as pGL3), is also insensitive to the action of hRev-erba. The effect of this nuclear receptor on the promoter for the human apo C-III gene is thus specific.

Figures 3 and 4 show that irrespective of the nuclear receptor cotransfected, hRev-erba reduces the activity of the reporter gene and that the effect of hRev-erba is dominant.

Figure 5 shows that the activity of the reporter gene decreases when the apo C-III promoter cloned upstream of it is gradually truncated. The activity of the promoter is lost between positions -108 and -62.

Figure 6 shows that the activity of the construct (-33/-16) 3XTkpGL3 is reduced by hRev-erba.

Figure 7 shows results of gel retardation experiments with labelled oligonucleotides which cover other fragments of the portion between the positions -198 and +24 of the promoter for the human apo C-III gene (for example with the double-stranded oligonucleotide corresponding to the fragment -104/-72 ("C3P-DR2") of the apo C-III promoter.

Figure 8A indicates that the mutation of the AGGTCA half-site present in position (-23/-18) of the human apo C-III promoter reduces the sensitivity of the entire promoter to hRev-erba by 50%. The effect of hRev-erba is totally lost when the construct -82/+24WTPGL3 is mutated. Figure 8B shows that mutation of the -23/-18 site in the construct (-33/-16WT) 3XTkpGL3 (to give the construct (-33/-16KO) 3XTkpGL3) suppresses its sensitivity to hRev-erba.

Figure 9 shows, surprisingly, that the P and γ Rev-erb isoforms also repress the activity of the construct -198/+24WTLuc+.

Figure 10A shows that a significant increase in the serum triglyceride concentration was observed in Rev-erb KO mutant mice compared with normal mice. Figure 10B shows that the increased expression is associated with a significant increase in the level of apo C-III in the plasma. Figure

10C shows that the expression of the mRNA coding for apo C-III is increased in mice whose Rev-erba gene has been destroyed by homologous recombination.

Figure 11 demonstrates a large increase in triglycerides in the VLDL fraction, as measured by

Figure 12 characterizes a construct comprising three copies of the Rev-DR2 site present in the promoter for the human Rev-erba gene, which are cloned before the Tk promoter.

Figure 13 depicts activity of the chimeras which combine the DNA binding domain of the yeast transcription factor Gal4 and the binding domain of the hRev-erba ligand and that of a reporter vector which comprises 5 copies of the Gal4 response element.

Please delete the paragraph on page 15, lines 23-24 and replace it with the following paragraph:

Table 1 collates the sequences of the oligo-nucleotides used **(SEQ ID NOS 1-29, respectively, in order of appearance)**.